

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.: 10/551,840
Confirmation No.: 4228
First-Named Inventor: Fabrizio Samaritani
Filing Date: January 20, 2006
Group Art Unit: 1654
Examiner: Anish Gupta
Attorney Docket No.: 007541-000006
Title: LIQUID PHARMACEUTICAL FORMULATIONS OF FSH AND LH
TOGETHER WITH A NON-IONIC SURFACTANT

DECLARATION OF DR. FABRIZIO SAMARITANI

I, Dr. Fabrizio Samaritani, hereby swear and affirm as follows:

1. I am over the age of eighteen (18) years and have held the position of formulation development department head in Serono International S.A. since 1996. A copy of my CV is attached as Exhibit 1.
2. I have more than 35 years of experience in the field of Pharmaceutical Technology. I have focused my work on development of parenteral dosage forms, more specifically on protein and peptide drug formulations.
3. I have authored or co-authored numerous publications in refereed journals regarding protein formulations. As detailed in Exhibit 1 attached hereto, I am also a named inventor on many patents.
4. I am a named inventor on the present patent application.
5. I am familiar with the disclosure and claims for the present application, U.S. Application Serial No. 10/551,840.

6. I have reviewed the final Office Action as well as the Advisory Action filed in the present application and the references cited therein, namely U.S. Patent application No. 2002/0165146 to Hoffmann et al. (hereinafter "Hoffmann"); and U.S. Patent No. 5,929,028 A1 to Skrabanja et al. (hereinafter "Skrabanja"). I have also reviewed the specification and the pending claims in the present application.

7. I understand that the present application has an earliest effective filing date of April 2, 2003. This Declaration describes the state of the art as I understood it while working in the field of protein formulation on and immediately before that date.

8. The present invention provides a liquid formulation of follicle stimulating hormone ("FSH"), optionally in combination with a luteinising hormone ("LH"), that is both preserved and stable and therefore is suitable as a multi-use medication. The addition of a preservative is a requirement by Regulatory Authorities for multi-use formulations.

9. The inventive preserved multi-use liquid formulation of the present application contains an FSH, and optionally LH, heterodimer in the presence of a poloxamer 188 surfactant and an m-cresol or phenol preservative, wherein the formulation is stable and avoids any precipitation. In my opinion, as of April, 2003, a person skilled in the art could not predict these results, nor would such a person have an expectation that such results could be achieved without further inventive work.

10. Previously, the prior art generally relied upon freeze-dried preparations in order to achieve the necessary level of stability and potency for FSH treatments. These freeze-dried preparations had to be reconstituted each time a dose was required – over and over again, day after day. Since FSH treatments typically require administration of FSH over several days, the

burden of repeated reconstitutions of dried preparations was considerable. There was therefore a substantial need for many years for a liquid FSH formulation that could be used over a period of days.

11. The existence of this long felt need is evidenced by the long standing (30+ years) sale of FSH formulations in the onerous form of a lyophilized powder requiring daily reconstitution for as many as 14 consecutive days. The art was struggling to solve a long-standing problem of FSH stability and it considered that formulating stable and preserved FSH solutions was extremely difficult. The present invention solved that need by providing a liquid formulation that is both preserved to keep it bacteria-free and stable due to careful selection of the surfactant, and therefore is a multi-use medication.

12. FSH, as a dimeric protein, is particularly unstable and sensitive to destabilizing effects/additives. In contrast to monomers, dimers may dissociate and this process may be fostered by excipients. In particular, at low concentrations FSH tends to dissociate. At high concentrations, FSH tends to aggregate. Any excipient present in a formulation potentially influences the aggregation and/or dissociation of FSH. This is in particular the case in the presence of organic solvents preservatives such as m-cresol and phenol. Therefore dimeric proteins such as FSH have *per se* a higher chance to be susceptible to destabilizing effects compared to monomeric proteins. This susceptibility to destabilizing effects is additionally increased for pure FSH, such as recombinant FSH, which is known by the person of skill in the art to be particularly unstable in solution. Both the cited references Hoffmann and Skrabanja confirm the difficulty of preparing stable protein formulations of FSH or the like.

13. An experienced formulator of therapeutic protein formulations recognized in 2003 that protein-preservative-surfactant compatibility is dependent upon the properties and interactions of each of the selected protein, preservative and surfactant chosen for a particular formula. Since protein, preservative and surfactant properties vary widely, compatibility is unpredictable without extensive experimentation. It remains common knowledge that the correlation between protein structure and stability is obscure. In consequence the prediction of protein stability in the presence of a particular preservative is still not possible, and was not possible at the time of the invention. The same holds true for the interactions between surfactants and preservatives which may lead to unwanted precipitation. The stability of an FSH formulation for any particular combination would need to be determined through extensive testing. The presence of a second dimeric protein LH increases the difficulty in formulating a stable, preserved and viable liquid solution of FSH, and adds the further requirement that the LH also remain stable and viable.

14. The use of poloxamer 188 in the present invention, in contrast to other surfactants, addresses instability whether due to surface adsorption or aggregation of FSH, or precipitation problems. It was found by the inventors that by formulating FSH and mixtures of FSH and LH with a Poloxamer 188 surfactant, a stable formulation is obtained that avoids the problem of precipitation in the presence of a preservative, such as m-cresol or phenol. By comparison, precipitation, resulting in the formation of turbid or milky solutions, occurs when Tween 20 is used with m-cresol or phenol.

15. Considering the state of the art knowledge in conjunction with the prior art cited by the Examiner, it is readily apparent that the cited prior art contains no teaching, motivation, or

suggestion to the skilled artisan that the state of the art differed from the knowledge that I have described above. It is apparent that the cited references contain no suggestion, motivation, or teaching to combine them in the manner suggested in the final Office Action. It is also apparent that the references do not provide any expectation of success with the inventive formulations of the present application.

16. Hoffman teaches FSH formulations and provides a long laundry list of a broad range of possible constituents, including preservatives, isotonicity agents, buffers, antioxidants and preservative enhancers. Hoffmann itself recognizes the difficulties of preparing stable protein formulations and shows that the effect on the stability of a selection of excipients, e.g., the specific preservatives claimed in Hoffmann, is not predictable. The examples in Hoffmann do not include formulations which contain excipients other than preservatives and buffers. In particular, no combination of preservative with surfactant is disclosed.

17. In my opinion, the laundry list of excipients in Hoffmann does not predict or suggest stability of an FSH solution (optionally containing LH) containing poloxamer 188 and a preservative selected from m-cresol and/or phenol, and would not have suggested such stability to a person of ordinary skill in the art in April, 2003.

18. The Skrabanja reference supports the foregoing statements. Skrabanja discloses that one of ordinary skill in the art would have known in 2003 that gonadotropins, particularly FSH, were unstable at low concentrations in solution. "The stability of proteins in aqueous formulations is generally a problem in [the] pharmaceutical industry. Likewise the stability of aqueous solutions of the gonadotropins is insufficient to allow storage for longer times. This is

especially true for preparations containing the very pure gonadotropins, prepared using recombinant DNA methods, in relatively dilute solutions.” Skrabanja, p. 2, lines 42-44.

19. Thus, while Skrabanja is cited in the final Office Action as teaching formulations of FSH and LH, Skrabanja also describes the substantial difficulty in preparing protein solutions. Consequently, Skrabanja does not teach that FSH and LH can successfully be combined with other excipients, except for the formulations specifically described in Skrabanja.

20. Skrabanja provides a unique stabilizing formula consisting of a polycarboxylic acid (such as citrate) or a salt thereof, and a thioether compound. This reference is very complete in that it describes the required and optional excipients in detail. Skrabanja does not teach or suggest that a preservative such as m-cresol or phenol could or should be added to Skrabanja’s FSH-containing formulation.

21. Thus, Hoffman deals with a specific issue for FSH formulations, namely, how to inhibit bacterial growth while still having a stable FSH solution. The answer from Hoffman is the use of particular preservatives. Skrabanja, on the other hand, is also concerned with the stability of FSH solutions but takes a totally different approach in that it makes the presence of polycarboxylic acid mandatory, but is completely silent on preservatives. Due to these very different approaches to stabilizing FSH formulations, the ordinarily skilled person would not have had any motivation to combine these references.

22. I believe that a person of ordinary skill in the art would not have combined Hoffman and Skrabanja as proposed in the final Office Action because (1) the references are not combinable, (2) any combination would not yield the claimed invention, and (3) nothing in the

references suggests stability and potency of FSH/LH when combined with the preservatives of Hoffman.

23. There is no direction to indicate which ones of the vast number of potential excipients listed in Hoffman and Skrabanja would be involved. These references do not provide a finite number of excipients, or of combinations of such excipients, from which to choose. Hoffman provides a laundry list, but its examples do not demonstrate their use. To the extent the excipients in Hoffman are cited with respect to stability, the reference is to inhibiting aggregation of the FSH. However, Skrabanja makes no mention of aggregation as a problem for its formulations. There is nothing from which to conclude how a person of ordinary skill in the art would choose to combine these different teachings.

24. Exhaustive lists of widely diverse components, as found in Hoffman and Skrabanja, do not direct a person of ordinary skill in the art to select particular combinations of functional components, and do not provide an expectation of success in the selection of such combinations. This is particularly true in the present situation, in view of the state of the art and the level of skill in the art of protein formulating.

25. If the ordinarily skilled person in the art had tried to combine the Hoffman and the Skrabanja references nevertheless, he would not have arrived at the presently claimed invention. The first solubilizer listed in Hoffman is Tween 20, which Skrabanja identifies as being especially preferred. A combination of these two references would thus have led automatically to an FSH formulation containing Tween 20. Such a formulation is not within the scope of the claimed invention; to the contrary, the present invention shows that FSH formulations containing

Tween 20 are not suitable as stable multi-use formulations as they lead in the presence of m-cresol or phenol to precipitation.

26. Further, assuming a combination of the Hoffman and Skrabanja references, then the resultant formulation at least would include a polycarboxylic acid or salt thereof, because the teaching from Skrabanja is that when FSH and LH are combined, then a special stabilizer system is required.

27. The results achieved by the claimed invention are not predictable. The invention does not represent a mere substitution of components providing the same functions. The function of any component within a pharmaceutical formulation is not predictable as the usefulness of that component to achieve the desired function depends not only on the characteristics of the component, but also on the characteristics and interactions of the other constituents of the formulation. Further, beyond achieving the desired functionality there is the potential for deleterious effects in other respects, e.g., turbidity.

28. In view of the complexities of pharmaceutical formulations, and the particular difficulties in preparing FSH solutions, there was no reasonable expectation for a person of ordinary skill in the relevant art, in April, 2003, that the claimed inventions would be successful in providing preserved and stable FSH formulations.

29. Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that all of the foregoing is true and correct. I have personal knowledge of the facts stated in this Declaration and, if called upon by a court of law to do so, I could and would testify competently to them.

30. I further declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and that these

statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both (18 U.S.C. § 1001), and may jeopardize the validity of the application or any patent issuing thereon.

Executed this 23 day of JUNE, 2009 at ROME.


Dr. Fabrizio Samaritani

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EDUCATION

1969 Degree in chemistry obtained from “Università degli studi di Roma”

WORK EXPERIENCE

1996- 2005 SERONO: Senior Manager, Formulation Development

- Head of the two functional groups:
 - Formulation Development
 - Production of Clinical Batches
- Developed injectable formulations of recombinant proteins, peptides and small molecules. Work focused on stabilizing proteins in solution and in solid state using biophysical techniques to characterize the protein structure: spectroscopy, circular dichroism, fluorescence, FTIR, calorimetry, ultracentrifugation.
- Built Serono's state-of-the-art in formulation development capabilities, managed implementation of compliance and regulatory capabilities. Designed and equipped laboratories. Hired managerial and technical staff.
- Consolidated the entire formulation process encompassing the introduction of new techniques as well as modification of existing protocols and data interpretation to allow timely and dependable formulation design.
- Process scaling-up, determination of critical parameters and process robustness, production of pre-clinical batches, pilot batches and clinical batches
- Experience of formulation development for monoclonal antibody and proteins at high concentration
- Experience of thermo-gels and spray-drying to obtain sustained release formulations

- Experience of registration file preparation and discussion with health authorities

Selected pharmaceutical products developed:

Gonal-F (r-FSH)

- Freeze-dried formulations monodose and multidose
- Liquid monodose and multidose presentations

Rebif (r-Interferon beta)

- Liquid formulation containing HSA
- Liquid formulation containing HSA free

Saizen (r-hGH)

- Freeze-dried multidose formulation
- Liquid multidose formulation

Serostim (r-hGH)

- Freeze-dried monodose formulation
- Liquid monodose formulation

Luveris (r-hLH)

- Freeze-dried monodose formulation
- Liquid monodose and multidose formulation

Ovitrelle (r-hCG)

- Freeze-dried monodose formulation
- Liquid monodose formulation

1980-1996 SERONO, Formulation Department Head

- Formulation studies for oral and topical formulations:
 - Tablets, sugar coated tablets, powders, granulates, syrups, suspensions, cream, gels etc...
 - Oral modified-release formulations of various types of drugs
- Formulation and technology of emulsions for oral and parenteral products
- Development of sterile formulations for urine derivative proteins and peptides

1970- 1980 SQUIBB, Scientist and Head of Formulation Development Lab

- ❑ Formulation development of oral and parenteral products
- ❑ Experience on cosmetic products developments
- ❑ Experience of antibiotic and vitamin based products

MAIN PATENT APPLICATIONS

- ❑ Pharmaceutical composition containing Gonadotropin comprising solid intimate mixture with stabilising amount of sucrose and other excipients
- ❑ Pharmaceutical compositions containing IL-6 and non reducing sugars such as sucrose and trehalose
- ❑ Stabilised interferon-beta liquid formulations with polyol, sugar or amino-acid
- ❑ Human Growth Hormone compositions stabilised with sucrose
- ❑ Stable liquid composition of Human Chorionic Gonadotropin
- ❑ GRF containing lyophilised pharmaceutical compositions
- ❑ Liquid formulations of Tumor Necrosis Factor Binding Proteins
- ❑ Liquid Growth Hormone formulations
- ❑ Liquid pharmaceutical formulations of FSH and LH together with a non ionic surfactant
- ❑ Freeze-dried FSH/LH formulations
- ❑ HSA-free stabilized Interferon liquid formulations
- ❑ Stabilized liquid protein formulations in pharmaceutical containers
- ❑ Stabilized Interferon liquid formulations

PERSONAL INFORMATION

Nationality: Italian, Age: 65

Personal interests:

- ❑ Travelling
- ❑ Sports: cycling, tennis
- ❑ Music